REMARKS

Applicants appreciate the courtesies extended to their representatives, Allan A. Fanucci and Teresa Chen, by Examiner Nathan W. Schlientz on July 7, 2009. The comments appearing herein are essentially the same as those presented and discussed during the interview.

Claims 1, 3-11, 13, 15-31, 37, 40-47 and 56-67, as amended, and new claim 68 are pending in this application for the Examiner's review and consideration. Claim 1 has been amended to recite preferred embodiments, i.e., when the active agent is testosterone, the testosterone is not used as the only active ingredient or if used as the sole active agent, the testosterone is present in an amount of 1% or less by weight of the formulation. Claim 1 has also been amended to delete the recitation of "tetraglycol furol." Claim 37 has been amended to incorporate features from claim 1 and claim 38, the latter of which has been cancelled. Claim 37 has also been amended to recite preferred embodiments, i.e., replacing "comprising" with "consisting essentially of." Claims 39 and 61 have been amended to depend from claim 37. Claims 64 and 66 have been amended in a similar manner to cover the preferred embodiments. New claim 68 is similar to claim 67 but dependent from claim 60. It is believed that no new issues are being raised by these amendments since diethylene glycol monomethyl ether was previously claimed in claim 60, a claim that is not amended in this response. Also, since no new matter has been introduced by any of these changes or additions, it should be entered at this time to place the claims in conditions for allowance and to reduce issues for appeal.

Claims 1, 5-7, 11 and 64 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by International Patent Application Publication No. WO 2002/011768 to Carrara et al. (referred to hereafter as "Carrara"). Carrara relates to a pharmaceutical formulation with good cosmetic properties and low irritation potential for the systemic treatment of diverse diseases by transdermal or transmucosal route, comprising as permeation enhancers defined amounts of fatty alcohols such as lauryl alcohol, n-decanol and oleyl alcohol in a ternary vehicle composite consisting of ethanol, propylene glycol and water, and optionally also a monoalkylether of diethylene glycol. As acknowledged by the Examiner, Carrara discloses a composition comprising 1.25 wt% testosterone. In contrast, claim 1 as amended now recites that when the formulation comprises testosterone, it is not used as the sole active agent or if it is the sole agent it is present in an amount of 1 wt% or less. As there is no teaching or suggestion in

Carrara to modify those comparative formulations, Carrara does not teach or suggest the presently claimed invention. Therefore, the rejection should be withdrawn.

Claims 1, 5, 6, 8-11, 13, 15-28, 37, 38, 40-47, 56-58 and 61-65 have been rejected under 35 U.S.C. 103(a) as unpatentable over US Patent No. 6,319,913 to Mak et al. (referred to hereafter as "Mak") in view of US Patent No. 5, 397,771 to Bechgaard et al. (referred to hereafter as "Bechgaard").

Mak discloses a transdermal and topical drug composition capable of enhancing the penetration of transdermally or topically applied drugs with reduced skin irritation that often accompanies transdermal and topical drug delivery. The composition of Mak is different from that of the present invention. As acknowledged by the Examiner, the composition of Mak uses oleic acid, a long chain fatty acid, which is specifically excluded from the composition of the present invention. As an attempt to remedy the deficiencies of Mak, Bechgaard is cited.

Although Bechgaard discloses a pharmaceutical preparation comprising an n-glycofurol for application of an effective amount of one or more biologically active substance(s) to a mucosal membrane of a mammal, claim 1 as amended now does not recite "tetraglycol furol." Thus, the rejection is rendered moot for claim 1 as well as claims 5, 6, 8-11, 13, 15-28, 64 and 65, which depend from claim 1. Regarding claim 37 and its dependent claims, neither Mak nor Bechgaard teaches or suggests a composition "consisting essentially of" the ingredients recited in claim 37. Therefore, the rejection over Mak and Bechgaard should be withdrawn.

Claims 1, 3-11, 13, 15-31, 37, 38, 40-47 and 56-67 have been rejected under 35 U.S.C. 103(a) as unpatentable over Mak in view of Bechgaard and further in view of US Patent No. 6,503,894 to Dudley et al. (referred to hereafter as "Dudley") in view of US Patent No. 5,955,455 to Labrie et al. (referred to hereafter as "Labrie").

As explained above, Mak and Bechgaard do not teach or suggest the present invention as claimed. Dudley and Labrie do not remedy the deficiencies of the primary references either. Dudley teaches a pharmaceutical composition useful for treating hypogonadism comprising an androgenic or anabolic steroid, a C1-C4 alcohol, a penetration enhancer such as isopropyl myristate, and water. Labrie teaches the treatment of vaginal atrophy, hypogonadism, diminished libido, loss of collagen or connective tissues in the skin using sex steroid precursors such as dehydroepiandrosterone and dehydroepiandrosterone sulphate.

There is no teaching or suggestion in either reference to motivate a person of ordinary skill in the art to replace the oleic acid in the composition of Mak with diethylene glycol monomethyl ether mentioned in Dudley, as suggested by the Examiner. More importantly, Mak specifically teaches that oleic acid is far superior than other permeation enhancers, including those closely related compounds such as oleyl alcohol in its ability to reduce skin irritation (col. 4, ll. 28-30 of Mak). Thus, Mak teaches away from the present invention by mandating the presence of oleic acid. Therefore, a person of ordinary skill in the art, following the teachings of Mak, will not even choose to replace the oleic acid in the composition of Mak with closely related compounds, let alone unrelated permeation enhancers such as diethylene glycol monomethyl ether mentioned by Dudley.

The Examiner is correct that Mak states that "(w)hile the combination of oleic acid and Carbopol 1342 produced very low irritating formulations, the incorporation of **other** irritation reducing agents can **further** decrease irritation" (col. 10, ll. 46-49 of Mak, emphasis added). However, such a statement only suggests adding additional irritation reducing agents, not replacing oleic acid with other agents. Accordingly, combining the teachings of the cited references, one of ordinary skill in the art will only arrive at a composition comprising both oleic acid and another permeation enhancer, the presently claimed formulation which is free of oleic acid.

During the interview, the Examiner indicated his disagreement with the prior explanation, stating that a skilled artisan might view Mak as at least suggesting that the other agents may be used to provide even less irritation. Applicants again respectfully traverse this statement, since there really is no teaching in Mak to remove the oleic acid and there is no suggestion in the other references to substitute anything else for it. Furthermore, as noted herein, Mak does not disclose or even list the preferred diethylene glycol monomethyl ether compound recited in the claims of the present invention.

Moreover, Dudley does not remedy this deficiency in Mak. Dudley neither teaches nor suggests using diethylene glycol monomethyl ether as a penetration enhancer that is capable of reduce skin irritation as presently claimed. As a matter of fact, Dudley merely mentions diethylene glycol monomethyl ether as one of numerous potential penetration enhancers (*see* col. 12, ll. 35-59 of Dudley), which is defined by Dudley as an agent known to accelerate the delivery of the drug through the skin, having the function of improving the solubility and diffusibility of

the drug and percutaneous absorption by changing the ability of the stratum corneum to retain moisture, softening the skin, improving the skin's permeability, acting as penetration assistants or hair-follicle openers or changing the state of the skin such as the boundary layer (*see* col. 12, ll. 23-34 of Dudley).

Although Dudley does mention other compounds such as diethylene glycol monomethyl ether in his listing of permeation enhancers, he attributes no preference for that compound. Instead, Dudley prefers fatty acid derivatives to other recited compounds. In particular, the examples of potential permeation enhancers recited in Dudley include C8-C22 fatty acids such as isostearic acid, octanoic acid, and oleic acid; C8-C22 fatty alcohols such as oleyl alcohol and lauryl alcohol; lower alkyl esters of C8-C22 fatty acids such as ethyl oleate, isopropyl myristate, butyl stearate, and methyl laurate; di(lower)alkyl esters of C6-C8 diacids such as diisopropyl adipate; monoglycerides of C8-C22 fatty acids such as glyceryl monolaurate, are all fatty acids (*see* col. 12, ll. 46-52 of Dudley). If a skilled artisan were to look to Dudley to remedy the deficiencies of Mak, they would most likely look to these compounds as potential substitutes for those of Mak.

Furthermore, Dudley has no disclosure that penetration enhancers are capable of reducing skin irritation. Instead, Dudley attributes the markedly reduced skin irritation of the AndroGel® formulation to the open system and the lower concentration of alcohol (*see* col. 48, ll. 30-59 of Dudley). As Dudley emphasizes the use of a permeation enhancer derived from a fatty compound, and in particular, isopropyl myristate, he certainly attributes no significance to the use of diethylene glycol monomethyl ether to reduce skin irritation, whereas the Applicants have shown that the formulation avoids undesirable odor and irritation from fatty compounds during use of the formulation, and the components of the delivery vehicle, including diethylene glycol monomethyl ether, facilitate absorption of the at active agent by the dermal or mucosal surfaces so that transfer or removal of the formulation from such surfaces is minimized. Instead, Dudley shows that AndroGel® formulation containing isopropyl myristate as the penetration enhancer causes minimal skin irritation (*see* col. 48, ll. 20-23 and Table 5 of Dudley), such that one of ordinary skill in the art, reading Dudley, will not be taught or motivated to select diethylene glycol monomethyl ether over isopropyl myristate.

Applicants further submit that the present claims are not derived from an "obvious to try" scenario based on the combination of Mak and Dudley. There are a large number of permeation

enhancing compounds disclosed in Dudley with no disclosure regarding which ones could lead to reduced skin irritation. Thus, a person of ordinary skill in the art does not have motivation or good reasons to look to Dudley for reduced irritation compounds. Instead, a skilled artisan would have to test within his or her technical grasp this multitude of compounds and evaluate the properties of each one before finding, unexpectedly, that some of those compounds might provide reduced irritation. Instead, the present invention relies on research and discovery rather than the application of ordinary skill and common sense to the prior art. The skilled artisan simply cannot vary all parameters or try each of numerous possible compounds until possibly arriving at the successful results of the present invention because the prior art gave no indication of which parameters were critical or important and further because no direction is given as to which compounds might provide the desired reduced skin irritation properties. As noted above, the claimed diethylene glycol monomethyl ether compound recited in the present claims is not specifically disclosed in Mak, and further, the compounds that are disclosed in Dudley do not include this compound as a preferred one for any reason.

In sum, the cited references do not render the present claims obvious. Thus, the rejection should be withdrawn.

Accordingly, it is believed that the entire application is now in condition for allowance, early notice of which would be appreciated. In the event that the Examiner does not agree that all claims are now allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues in an effort to expedite the eventual allowance of this application.

Respectfully submitted,

8/31/09
Date

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